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(72) Inventors GEORGE EDWARD DAVIES and THOMAS PATERSON JOHNSTON

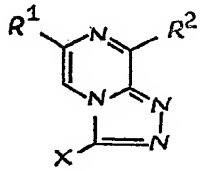
(54) PHARMACEUTICAL COMPOSITIONS

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to the treatment of bronchospasm, and in particular it relates to pharmaceutical compositions which are capable of preventing bronchospasm and are therefore useful in the treatment of diseases which involve spasm or constriction of the bronchial musculature, for example asthma or bronchitis.

It is known that sympathomimetic amines, for example isoprenaline or adrenaline, are capable of preventing bronchospasm when administered to a host. It has now been found that certain s-triazolo[4,3-a]pyrazine derivatives, which themselves are capable of preventing bronchospasm, potentiate the action of sympathomimetic amines so that the combined effect of a sympathomimetic amine and a s-triazolo[4,3-a]pyrazine, as hereinafter defined, in preventing bronchospasm is much greater than the sum of the effects of the individual components.

According to the invention there is provided a method of preventing bronchospasm in animals excluding man which comprises administering to the animal a sympathomimetic amine in conjunction with an s-triazolo[4,3-a]pyrazine of the formula:—



wherein R^1 and R^2 stand for alkyl radicals of 1—4 carbon atoms, and X stands for an amino, hydroxy, formamido or acetamido radical.

Preferred s-triazolo[4,3-a]pyrazine derivatives are, for example, 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine and 3-amino-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine.

Depending upon the biological properties of the sympathomimetic amine, the s-triazolo[4,3-a]pyrazine may be administered together with the sympathomimetic amine in the form of a pharmaceutical composition containing both components or it may be administered separately from the sympathomimetic amine. Thus when the sympathomimetic amine is only effective when administered by inhalation, for example adrenaline or isoprenaline, the s-triazolo[4,3-a]pyrazine may be administered by the use of an aerosol containing both components, or preferably, by oral administration at approximately the same time as the sympathomimetic amine is administered by inhalation. When the sympathomimetic amine is effective by oral or parenteral

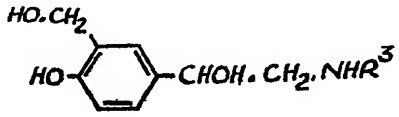
administration, a preferred method of administration is by the use of a pharmaceutical composition comprising both components, for example a tablet, capsule, solution or suspension, although separate administration is possible.

The exact proportion of sympathomimetic amine to s-triazolo[4,3-a]pyrazine to be administered in order to produce the best result will depend upon the individual patient and the components used. However, in general, the amount of sympathomimetic amine administered should be from 0.1% to 5.0% by weight of the amount of s-triazolo[4,3-a]pyrazine administered, and the total amount of material administered should be from 0.5 mg./kg. to 5.0 mg./kg. as and when required by the patient.

According to a further feature of the invention, there is provided a pharmaceutical composition comprising a sympathomimetic amine which shows bronchodilator activity when administered orally or parenterally, together with an s-triazolo[4,3-a]-pyrazine as defined above, and a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical composition may be in a form suitable for oral administration, for example a tablet, capsule, solution or suspension, or it may be in a form suitable for parenteral administration, for example a sterile, injectable solution or suspension. The composition may be manufactured by employing conventional techniques and by using conventional excipients. A dosage form, tablet, capsule or specified volume of a liquid formulation should contain a total of from 10 mg. to 100 mg. of sympathomimetic amine and s-triazolo[4,3-a]pyrazine, and of this total, the sympathomimetic amine should form from 0.5% to 5% by weight.

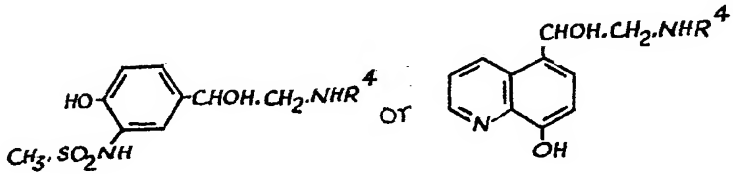
A particularly suitable sympathomimetic amine which may be used in a pharmaceutical composition of the invention because of its potent action upon bronchial muscle and relatively weak action upon cardiac muscle, is a 2-amino-1-phenylethanol derivative of the formula:—



wherein R^3 stands for a branched-chain alkyl radical of up to 6 carbon atoms optionally substituted by a phenyl, phenoxy, hydroxyphenyl, methoxyphenyl or morpholino radical, or a pharmaceutically-acceptable acid addition salt thereof. Of these 2-amino-1-phenylethanol derivatives, a particularly preferred compound is that wherein R^3 stands for the t-butyl radical.

When such a 2-amino-1-phenylethanol derivative is used in a pharmaceutical composition of the invention, it should form from 0.5% to 5.0% by weight of the s-triazolo[4,3-a]pyrazine, and a dosage form for the treatment of asthma should contain a total of from 10 mg. to 100 mg. of the active ingredients.

Other suitable sympathomimetic amines which may be used in a pharmaceutical composition of the invention are compounds of the formula:—



wherein R^4 stands for a branched-chain alkyl radical of up to 6 carbon atoms, for example an isopropyl or t-butyl radical. These compounds may be used in the compositions of the invention in the same way as the 2-amino-1-phenylethanol derivatives described above.

The invention is illustrated but not limited by the following Examples.

Example 1

A mixture of 25 parts of 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]-pyrazine, 0.25 part of 2-(t-butylamino)-1-[(4-hydroxy-3-hydroxymethyl)phenyl]-

ethanol (optionally as its hydrochloride), 65 parts of maize starch, 130 parts of calcium phosphate and 1 part of magnesium stearate is compressed, and the compressed mixture is then broken down into granules by passage through a 16-mesh screen. The resultant granules are then compressed into tablets each containing a total of 25 mg. of the active ingredients.

EXAMPLE 2

A normal guinea-pig lung was removed from the animal and mounted in the apparatus described by Bhattacharya and Delaunois (Arch. int. pharmacodyn. 1955, *101*, 495). The lung was perfused with Tyrode's solution containing 3% dextran at a rate of 2.0 ml. per minute, while at the same time being artificially respired by a pump delivering 9 ml. of air per stroke and running at 22 strokes per minute. Pressure changes in the air in the trachea were measured with a pressure transducer connected to a recording device, and so bronchospasm induced by the presence of acetylcholine in the perfused fluid could be measured. Test compounds were added to the Tyrode's solution being perfused through the lung, and acetylcholine was added at 4-minute intervals after the addition of the test compound. The degree of bronchospasm produced by the acetylchlorine was measured and compared with the degree of bronchospasm produced by acetylcholine in the absence of a test compound.

The following results were obtained:—

	Treatment	Percentage bronchospasm
	acetylcholine, 2.5 μg.	97
A.	2-(t-butylamino)-1-[(4-hydroxy-3-hydroxy-methyl) phenyl]ethanol, 0.05 μg. Challenged with acetylcholine, 2.5 μg. after:—	
	4 minutes	64
	8 minutes	78
	12 minutes	87
B.	3-acetamido-6-methyl-8-n-propyl-s-triazolo-[4,3-a]pyrazine, 5 μg. Challenged with acetylcholine 2.5 μg. after:—	
	4 minutes	89
C.	2-(t-butylamino)-1-[(4-hydroxy-3-hydroxy-methyl)phenyl]ethanol, 0.05 μg. together with 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine, 5 μg. Challenged with acetylcholine 2.5 μg. after:—	
	4 minutes	24
	8 minutes	45
	12 minutes	63
	16 minutes	74
	20 minutes	75
	24 minutes	71
	28 minutes	72
	32 minutes	88

Treatment		Percentage bronchospasm
D.	In a separate experiment, 2-(t-butylamino)-1-[(4-hydroxy-3-hydroxymethyl)phenyl]ethanol, 0.2 μg. Challenged with acetylcholine after:—	
	4 minutes	46
E.	3-acetamido-6-methyl-8-n-propyl-s-triazolo-[4,3-a]pyrazine, 20 μg. Challenged with acetylcholine after:—	
	4 minutes	88

From the above data it is clear that treatment with a combination of both drugs, C, produced a greater and more presistent effect than treatment with either component at the same dose, A or B, or at 4 times that dose, D or E.

5 EXAMPLE 3 5

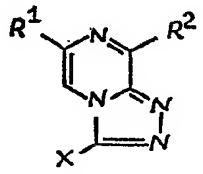
The procedure described in Example 2 was repeated and the results expressed as the percentage inhibition of acetylcholine-induced bronchospasm produced by the test compound at a given interval after administration of the test compound. The following results were obtained.

Test compound		Challenged with acetylcholine 2.5 μg.	
		Time	Percentage inhibition of bronchospasm
A.	isoprenaline, 0.005 μg.	4 min.	0
B.	3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine, 5 μg.	4 min. 8 min.	11 5
C.	isoprenaline, 0.005 μg. together with 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine, 5 μg.	4 min. 8 min. 12 min.	61 26 24
D.	isoprenaline, 0.01 μg.	4 min. 8 min.	14 3
E.	adrenaline, 0.05 μg.	4 min. 8 min. 12 min.	34 20 13
F.	3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine, 5 μg.	4 min.	8
G.	adrenaline, 0.05 μg. together with 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine, 5 μg.	4 min. 8 min. 12 min.	75 54 36
H.	adrenaline, 0.1 μg.	4 min. 8 min.	67 29

The above results show that treatment with a mixture of both drugs, C and G, produced a greater and more persistent effect than treatment with either component at the same dose, A or B, or E or F, or with sympathomimetic amine at twice that dose D or H.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition which comprises a sympathomimetic amine which shows bronchodilator activity when administered orally or parenterally, together with an s-triazolo[4,3-a]pyrazine derivative of the formula:—



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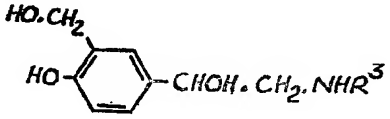
wherein R^1 and R^2 stand for alkyl radicals of 1—4 carbon atoms, and X stands for an amino, hydroxy, formamido or acetamido radical.

2. A composition as claimed in claim 1 wherein the s-triazolo[4,3-a]pyrazine derivative is 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine.

3. A composition as claimed in claim 1 wherein the s-triazolo[4,3-a]pyrazine derivative is 3-amino-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine.

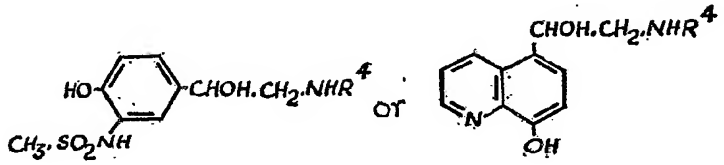
4. A composition as claimed in claim 1, 2 or 3 wherein the sympathomimetic amine is a 2-amino-1-phenylethanol derivative of the formula:—



wherein R^3 stands for a branched chain alkyl radical of up to 6 carbon atoms optionally substituted by a phenyl, phenoxy, hydroxyphenyl, methoxyphenyl or morpholino radical, or a pharmaceutically-acceptable acid addition salt thereof.

5. A composition as claimed in claim 4 wherein R^3 stands for the t-butyl radical.

6. A composition as claimed in 1, 2 or 3, wherein the sympathomimetic amine is a compound of the formula:—



wherein R^4 stands for a branched-chain alkyl radical of up to 6 carbon atoms.

7. A composition as claimed in any preceding claim, wherein the amount of sympathomimetic amine present is from 0.5% to 5% by weight of the amount of s-triazolo[4,3-a]pyrazine derivative.

8. A composition as claimed in claim 9 in which a dosage form contains a total of from 10 mg. to 100 mg. of sympathomimetic amine and s-triazolo[4,3-a]pyrazine taken together.

9. A pharmaceutical composition which comprises 2-(t-butylamino)-1-[(4-hydroxy-3-hydroxymethyl)phenyl]ethanol, optionally in the form of its hydrochloride, together with 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine, and a pharmaceutically-acceptable diluent or carrier.

10. A composition as claimed in claim 9 wherein the amount of 2-(t-butylamino)-1-[(4-hydroxy-3-hydroxymethyl)phenyl]ethanol present is from 0.5% to 5% by weight of the amount of 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine, and in which a dosage form contains a total of from 10 mg. to 100 mg. of 2-(t-butylamino)-1-[(4-hydroxy-3-hydroxymethyl)phenyl]ethanol and 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine taken together.

11. A composition as claimed in claim 10 which is in the form of a tablet or capsule.

12. A method of preventing bronchospasm in animals excluding man which comprises administering to the animal a sympathomimetic amine in conjunction with an s-triazolo[4,3-a]pyrazine derivative of formula I in claim 1, wherein R^1, R^2 and X have the meanings stated in claim 1.

13. A method as claimed in claim 12 wherein the amount of sympathomimetic amine administered is from 0.1% to 5% by weight of the amount of s-triazolo-[4,3-a]pyrazine administered, and the total amount of both ingredients is from 0.5 mg./kg. to 5 mg./kg.

14. A pharmaceutical composition as claimed in claim 10, substantially as described in Example 1.

A. H. LAIRD,
Agent for the Applicants.

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